**Does current research evidence indicate the need to conduct serum investigation(s) for ischaemic lesions in acute intracerebral haemorrhage work-up?**

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**Short title:** Serum Biomarkers and DWI Lesions After Intracerebral Haemorrhage

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**Keywords:** Intracerebral haemorrhage (ICH), Biomarkers, Diffusion-weighted imaging (DWI), Cerebral ischaemia

## Abstract

**Background:** Ischaemic injury occurring in association with acute intracerebral haemorrhage (ICH) is increasingly recognised, most commonly as remote diffusion-weighted imaging (DWI) lesions. However, the mechanisms, timing, and clinical significance of these lesions remain incompletely defined. This narrative review evaluates whether current evidence supports serum biomarker testing as part of the acute work-up for ischaemic lesions after ICH.

**Summary:** We distinguish diagnostic utility (identifying or predicting lesions) from prognostic utility (predicting outcomes). Candidate biomarkers are narratively appraised by assessing: (i) evidence linking circulating levels to magnetic resonance imaging (MRI)-defined remote DWI lesions, (ii) mechanistic alignment with post-ICH microvascular injury, and (iii) limitations of the available clinical evidence. Across astrocytic and neuronal injury markers (glial fibrillary acidic protein (GFAP), S100 calcium-binding protein B (S100B), neurofilament light chain (NfL)) and systemic inflammatory indices (C-reactive protein (CRP), neutrophil–lymphocyte ratio (NLR)), the prevailing signal reflects global injury burden or the differentiation between haemorrhagic and ischaemic stroke subtypes rather than lesion-specific detection. Lactate dehydrogenase (LDH) has demonstrated direct association with remote lesions in a retrospective ICH cohort but lacks brain specificity and is vulnerable to extracranial confounding. Prognostic biomarkers (inflammatory, oxidative, and haemostasis-related) predict general ICH outcomes but are yet to be validated for risk stratification specifically in patients with secondary DWI lesions.

**Key Messages:** Overall, no single serum biomarker currently justifies routine clinical testing to detect or guide management of remote DWI lesions after ICH. Future work should prioritise temporally resolved, multi-marker panels validated against serial MRI-defined lesion phenotypes to characterise the ischaemic phenotype and support precision haemodynamic and anti-inflammatory strategies.

## Introduction

Stroke was the third leading cause of death globally in 2021 [1–4]. Intracerebral haemorrhage (ICH) remains the least treatable stroke subtype and a major contributor to stroke-related mortality and disability worldwide [1].

## Pathophysiology and risk factors for ICH

The pathophysiology of ICH is important for understanding the risk factors associated with its aetiologies. The pathophysiology of ICH can be broadly divided into primary injury and secondary downstream mechanisms of injury. Primary injury reflects haematoma expansion and the mass effect of the initial haematoma. Secondary injury arises from a range of processes, including inflammation, vasogenic oedema, oxidative stress, and the accumulation of haemoglobin breakdown products [5]. The European Stroke Organisation (ESO) (2025) highlight that haematoma expansion has been associated with worse outcomes in ICH [6].

The causes of ICH can be broadly categorised according to underlying vascular pathology. Microvascular causes include hypertensive arteriolosclerosis and cerebral amyloid angiopathy [6, 7], whereas structural or macrovascular causes include vascular malformations, tumours, aneurysms, and cavernomas [4, 6, 7].

## Current acute ICH investigative 'work-up'

Current international guidelines prioritise early diagnosis and stabilisation [6,7]. Initial work-up includes a focused history, examination, and urgent non-contrast computed tomography (CT) of the head to differentiate ICH from ischaemic stroke. Following diagnosis and acute stabilisation, secondary investigations such as CT angiography (CTA) and magnetic resonance imaging (MRI) are suggested to identify the underlying cause and guide management strategies [6, 7, 8].

Blood pressure lowering is a cornerstone of acute ICH management, and current guidelines recommend early reduction in systolic blood pressure [6,7]. However, large randomised controlled trials, including INTERACT2 [9,10] and ATACH-II [30], have highlighted the importance of avoiding excessive or rapid blood pressure reductions. Although these trials did not demonstrate a clear increase in MRI-defined cerebral ischaemia, secondary analyses suggest that substantial systolic blood pressure drops (e.g., >60-70 mmHg) may be associated with worse clinical outcomes, and ATACH-II reported increased renal adverse events at lower blood pressure targets. These findings have raised concerns regarding potential impairment of cerebral perfusion in vulnerable perihaematomal or remote territories [6,8,11,17]. More recently, the INTERACT3 trial emphasised a bundled, multimodal approach to ICH management, combining early blood pressure lowering with glycaemic control, temperature regulation, and reversal of anticoagulation [35].

## Ischaemic lesions and current recommendations

Ischaemic lesions after ICH have emerged as an area of increasing research interest. Brain ischaemia is both a risk factor for ICH and a common sequela, as patients with ICH are at a greater risk of subsequent ischaemic stroke. This is hypothesised to be due to the overlapping cardiovascular risk factors but may also relate to local mass effect from the haematoma causing compression of adjacent small and medium-sized vessels, impaired microvascular perfusion, and regional hypoperfusion in the perihaematomal territory [11-14]. Acute vascular events are also a frequent cause of hospital readmission after ICH, with up to 41% of patients developing ischaemic infarction during the acute course [10, 15, 16].

Ischaemic lesions can be identified on MRI, although the underlying pathophysiology of ischaemic lesions and the specificity of imaging in the detection of them remains uncertain. Diffusion-weighted imaging (DWI) is a specific sequence of MRI used to detect these ischaemic lesions. MRI-defined diffusion-restricted lesions have been found in up to 40% of ICH patients [16]. These MRI-defined diffusion-restricted lesions have been associated with a 2.5-fold increased risk of subsequent stroke and worse functional outcomes [16, 17], supported by findings from Posener et. al. in a meta-analysis systematic review [19]. However, not all DWI lesions represent new ischaemic injury [18]. Some lesions may be pre-existing and have been identified on baseline imaging [16, 19]. Furthermore, antihypertensive therapy appears to have a limited effect on DWI lesion burden [16].

Neither the American Heart Association (AHA), the American Stroke Association (ASA) nor ESO guidelines currently recommend routine DWI for the detection of ischaemic lesions [6,7]. This reflects ongoing uncertainty regarding both the detection and clinical significance of these lesions [16, 21]. Similarly, the optimal blood pressure management strategy in acute ICH remains unresolved. This uncertainty has led to increasing interest in serum biomarkers as potential complementary tools [118].

One might question the need for a serum biomarker if remote DWI lesions can be seen on MRI. However, MRI is not routinely performed in all patients with acute ICH and is not required by current guidelines for detecting secondary ischaemic lesions [6,7]. In addition, diffusion-restricted lesions may evolve over time and may not be captured on a single scan [15-19]. A circulating biomarker, if validated, could therefore support early risk stratification and complement imaging, rather than replace it.

Several recent reviews have examined biomarkers, secondary brain injury, and the broader pathophysiology of ICH [21,69,70]. However, none have specifically evaluated circulating

biomarkers in relation to MRI-defined remote DWI lesions after ICH or examined whether current evidence supports serum investigation for this distinct imaging phenotype. This review addresses that gap by distinguishing diagnostic utility (identification or prediction of remote DWI lesions) from prognostic utility (prediction of clinical outcomes) while critically evaluating the biological and methodological barriers that currently limit clinical translation.

## Serum biomarkers and rationale for investigation

Candidate markers have been proposed for diagnostic use in ICH, for the assessment of cerebral oedema, as predictors of prognosis, and as indicators of underlying aetiology [21]. The biological rationale stems from pre-clinical studies demonstrating that secondary brain injury after ICH is accompanied by systemic inflammatory responses. Parenchymal blood is associated with multiple injury pathways involving thrombin release, red blood cell lysis, ischaemia, and neuronal death. These processes may promote microglial activation, neutrophil infiltration, and oxidative stress, resulting in the release of inflammatory mediators into the circulation, which may contribute to downstream signalling, blood brain barrier (BBB) disruption, and oxidative stress [22-29].

While these mechanisms provide a rationale for biomarker investigation in ICH broadly, their relevance to remote DWI lesions remains uncertain. A major challenge in developing biomarkers for remote DWI lesions after ICH is the incomplete understanding of their underlying biology. Although these lesions are increasingly recognised, their pathogenesis and clinical significance remain uncertain [15,16,18,19]. Proposed mechanisms include microinfarction, haemodynamic compromise, endothelial dysfunction, thrombo-inflammatory injury, and manifestations of underlying cerebral small vessel disease [5,15,16,18-20]. Consequently, it remains unclear whether a single unifying biological pathway exists that could be captured by a circulating biomarker. Furthermore, many candidate biomarkers discussed in this review were originally developed and validated in different clinical contexts, including acute ischaemic stroke, haemorrhagic transformation, and stroke subtype differentiation [31-34,41,56-60]. As remote DWI lesions after ICH may represent a distinct biological process, biomarker performance cannot be assumed to translate across these settings. These factors should be considered fundamental limitations when interpreting the current evidence.

## Review Objectives

ICH initiates secondary injury pathways beyond the local haematoma that may be reflected in peripheral serum markers. This review evaluates current evidence for serum biomarkers in

relation to ischaemic lesions after ICH, structured around two domains: diagnostic utility (identification or prediction of MRI-defined lesions) and prognostic utility (risk stratification and outcome prediction).

It does not simply ask whether serum biomarkers can detect DWI lesions after ICH. Rather, it examines why current biomarker strategies have not demonstrated lesion-specific diagnostic utility, and what these reveals about key biological and methodological gaps.

Candidate biomarkers are organised by biological domain and appraised against imaging-defined remote DWI lesions, considering mechanistic alignment and strength of evidence.

## Review Methods

This article was conducted as a narrative review and prepared in accordance with principles outlined in the Scale for the Assessment of Narrative Review Articles (SANRA) [117]. A structured search of PubMed/MEDLINE, Embase, and Scopus was undertaken to identify studies evaluating circulating biomarkers in ICH, with particular focus on MRI-defined DWI lesions and secondary cerebral ischaemia.

Search terms included combinations of keywords relating to ICH, DWI lesions, cerebral ischaemia, and candidate biomarkers. Reference lists of relevant studies and reviews were also screened for additional publications. Human studies evaluating biomarker associations with ICH, DWI lesions, or clinical outcomes were prioritised, while mechanistic studies were included where relevant to biological interpretation.

## Diagnostic utility of serum markers

In this review, *'diagnostic utility'* refers specifically to whether a circulating biomarker can identify, predict, or biologically align with imaging-defined secondary ischaemic injury after acute ICH. This is distinct from the *prognostic utility* of biomarkers to predict mortality or functional outcome, which is addressed separately.

To assess diagnostic utility, we focus on whether a circulating biomarker can inform clinical decision making regarding secondary ischaemic injury after ICH, including risk stratification for remote DWI lesions, prioritisation of MRI, and identification of patients at risk of microvascular perfusion failure during acute management. For each biomarker, we evaluate:

i. Evidence for association with imaging defined secondary ischaemic lesions after ICH
ii. Mechanistic alignment with the pathophysiology of remote microinfarction
iii. The strength and limitations of available clinical evidence.

## 1. Astrocytic and neuronal injury markers

### *Plasma glial fibrillary acidic protein (GFAP)*

Glial fibrillary acidic protein (GFAP) is an astrocytic intermediate filament and cytoskeletal protein that is typically near undetectable in peripheral blood under physiological conditions. It is released following astroglial necrosis and membrane disruption [21, 36]. In acute ICH, rapid mechanical tissue disruption and early BBB failure during haematoma formation and expansion are thought to contribute to early GFAP appearance in blood. Whereas in acute ischaemic stroke, GFAP release is delayed, mirroring the slower evolution of necrotic cell death and BBB disruption [21, 31, 36].

To date, no previous studies have directly evaluated serum GFAP for the identification or prediction of imaging-defined secondary ischaemic injury after ICH. The clinical evidence-base instead supports GFAP as a hyperacute stroke-subtype biomarker, with a diagnostic window in the first hours after symptom onset in which GFAP is relatively high in ICH, and low or undetectable in ischaemic stroke, enabling differentiation of haemorrhage from infarction in emergency pathways [31, 36, 37, 38, 39, 56, 57, 58]. In the DETECT LVO analysis, integrating point-of-care GFAP with established clinical large vessel occlusion (LVO) scores improved discrimination for LVO by reducing misclassification driven by ICH among patients with severe stroke syndromes [41]. These data reinforce that GFAP has the strongest clinical traction as a rapid marker of haemorrhage diagnosis in undifferentiated acute stroke, rather than as a biomarker for lesion-specific secondary cerebral ischaemia once ICH is established.

In addition, reported GFAP cut-offs are platform- and intended-use specific, and therefore should not be treated as transferable thresholds for post-ICH secondary ischaemic lesion detection. DETECT LVO used point-of-care GFAP testing within a prehospital triage framework, whereas TIME validated a fixed GFAP threshold within a combined biomarker scale decision rule. These cut-offs support stroke-subtype classification and do not establish lesion-specific diagnostic utility for remote DWI lesions after ICH [41, 57, 65].

Mechanistically, GFAP is aligned with astroglia structural destruction and BBB disruption occurring early with haemorrhage-related tissue injury, rather than the delayed microvascular processes, such as microvascular perfusion failure and endothelial dysfunction, hypothesised to underlie remote DWI after ICH [36, 41]. Therefore, while GFAP plausibly tracks the presence and extent of primary haemorrhagic injury, it does not map cleanly onto the spatially

remote and often delayed microinfarction phenotype represented by DWI lesions after ICH [36, 41].

Overall, despite strong validation as a biomarker of haemorrhage presence in hyperacute stroke triage, at present, GFAP should not be considered a diagnostic serum marker for secondary ischaemic lesions after ICH. MRI-linked prospective studies would be required to demonstrate any incremental diagnostic value for predicting new DWI lesions beyond established clinical and imaging predictors [31, 36, 56, 58]. Therefore, current evidence does not support GFAP as a lesion-specific biomarker for identifying remote DWI lesions after ICH.

### *S100 calcium-binding protein B*

S100B is a calcium-binding protein predominantly expressed by astrocytes and is released into the circulation in response to astrocytic stress, neuroinflammation, and BBB permeability changes, with low circulating concentrations under physiological conditions [21, 34, 36, 42].

No previous studies have directly examined serum S100B as a marker for imaging-defined secondary ischaemic lesions after acute ICH. Prior work has mainly evaluated S100B for stroke subtype differentiation, but performance is consistently inferior to GFAP and lacks robustness across settings [42]. In hyperacute plasma proteomic profiling comparing ischaemic stroke and ICH, GFAP showed the strongest discriminative signal, whereas S100-family proteins demonstrated more variable expression and limited diagnostic performance [43].

Mechanistically, S100B is biologically aligned with astrocytic activation and general CNS injury signalling rather than the microvascular perfusion failure and thrombo-inflammatory processes hypothesised to generate remote DWI lesions after ICH [21, 34, 42]. This broad injury responsiveness plausibly limits lesion specificity and reduces its potential utility for detecting focal secondary ischaemic phenomena.

Overall, current evidence does not support S100B as a diagnostic serum marker for post-ICH secondary ischaemic lesions. Any future role would require serial sampling linked to MRI-defined new lesion phenotypes to determine whether specific temporal patterns add incremental diagnostic information. Therefore, current evidence does not support S100B as a biomarker for identifying remote DWI lesions after ICH.

### *Neurofilament light chain (NfL)*

Neurofilament light chain (NfL) is a cytoskeletal structural protein enriched in large, myelinated axons and is released following neuroaxonal injury, making circulating serum NfL (sNfL) a sensitive marker of neuronal damage across multiple neurological disorders [61,62].

In acute cerebrovascular events, sNfL reflects the magnitude of axonal injury and typically demonstrates delayed kinetics relative to the initiating insult [61, 62].

No previous studies have directly linked circulating sNfL to imaging-defined secondary ischaemic lesions remote from the haematoma after acute ICH. Existing work shows that sNfL is elevated in both ischaemic and haemorrhagic stroke and correlates with clinical severity and outcome, and in ICH correlates with haemorrhage severity features, such as haematoma volume and intraventricular extension [61, 62]. These associations support prognostic relevance but do not establish lesion specific diagnostic utility for post-ICH microinfarction.

Mechanistically, sNfL represents downstream axonal degeneration and cumulative neural injury burden rather than the upstream microvascular and endothelial mechanisms proposed to contribute to remote DWI lesions after acute ICH [61, 62]. Its lack of spatial specificity and delayed rise limit its plausibility as a marker for identifying focal imaging-defined secondary ischaemic lesions in the hyperacute or early subacute period.

In summary, current knowledge suggests that sNfL should be viewed as a sensitive marker of overall neuroaxonal injury and prognosis rather than a diagnostic biomarker for post-ICH secondary ischaemic lesions. MRI-linked studies with serial sampling would be required to determine whether specific trajectories can discriminate lesion phenotypes. Accordingly, serum NfL should not currently be considered a lesion-specific biomarker for remote DWI lesions after ICH.

## 2. Other inflammatory and immune-related markers

### *C-reactive protein (CRP) & Interleukins (IL)*

CRP is an acute-phase reactant synthesised by hepatocytes downstream of interleukin-6 (IL-6) signalling and reflects integrated systemic inflammation [44, 49]. In acute ICH, CRP elevation likely reflects systemic and neuroinflammatory activation occurring in the context of BBB disruption, haemoglobin breakdown products, and microglial/endothelial activation [44, 49].

No previous studies have directly evaluated CRP as a diagnostic marker for imaging-defined remote DWI lesions after ICH. Although elevated CRP is frequently observed and has been associated with worse outcomes in ICH cohorts, these associations reflect global inflammatory burden and illness severity rather than lesion-specific detection of remote diffusion restriction [44, 45, 46, 47].

The mechanism of CRP is biologically distal from the microvascular and endothelial processes thought to underlie remote DWI lesions, after ICH. As a downstream integrative inflammatory

marker, it lacks spatial specificity and is highly susceptible to extracranial confounding, limiting its diagnostic relevance for focal cerebral ischaemia [47].

By contrast, upstream inflammatory mediators may have closer mechanistic alignment with post-ICH microvascular injury. The IL-1β–IL-6 axis has been implicated in endothelial dysfunction, impaired cerebral autoregulation, microvascular thrombosis, and leukocyte adhesion, providing biological plausibility for a link to secondary ischaemic lesions [47]. Experimental animal model work has identified cold-inducible RNA-binding protein as a neuron-derived damage-associated molecular pattern-activating microglial inflammation via IL-6 receptor–STAT3 signalling. This supports pathway-level plausibility for inflammation-mediated secondary injury [49]. Separately, systematic review evidence suggests IL-1 receptor antagonism may improve outcomes in acute stroke [50] and translational reviews support inflammatory amplification after ICH [51] However, despite strong biological plausibility, no human studies have demonstrated that circulating IL-pathway markers identify or predict MRI-defined secondary ischaemic lesions after ICH.

Overall, CRP should be regarded as a non-specific inflammatory marker without diagnostic utility for post-ICH secondary ischaemic lesions. Upstream IL-pathway mediators remain hypothesis-generating candidates but currently lack lesion-specific validation, Consequently, neither CRP nor circulating interleukin markers can currently be recommended for identifying remote DWI lesions after ICH.

### *Neutrophil-Lymphocyte Ratio (NLR)*

The neutrophil–lymphocyte ratio (NLR) is a peripheral marker reflecting the balance between innate immune activation and adaptive immune suppression [52, 53]. NLR is readily available and time-sensitive, but it is not specific to the brain or its MRI-defined diffusion-restricted lesions.

No previous studies have directly correlated NLR with imaging-defined secondary ischaemic lesions after acute ICH. In a post hoc analysis of the CLEAR III trial, serial NLR values were associated with short-term systemic complications after ICH and intraventricular haemorrhage, with higher baseline/day-3 NLR associated with infectious complications and higher day-5 NLR associated with thrombotic events including cerebral infarction and venous thromboembolism [53]. These associations suggest biological relevance to thrombotic-inflammatory risk but do not establish MRI lesion-specific diagnostic performance.

Mechanistically, NLR plausibly aligns with thrombotic-inflammatory processes implicated in microvascular dysfunction after ICH, including neutrophil-mediated endothelial injury, tissue

factor expression, platelet activation, and prothrombotic states, all of which could contribute to remote diffusion restriction [52-54]. However, NLR is highly nonspecific and influenced by infection, stress responses, and comorbidity, limiting its value as a standalone diagnostic tool for lesion detection.

Overall, NLR should not be considered a diagnostic serum marker for post-ICH secondary ischaemic lesions but may have value as a component of a temporally resolved biomarker panel capturing thrombo-inflammatory activation. However, NLR alone cannot currently be considered a diagnostic biomarker for remote DWI lesions after ICH.

### *Matrix metalloproteinases (MMP-9)*

Matrix metalloproteinase-9 (MMP-9) is a zinc-dependent endopeptidase that contributes to BBB disruption through degradation of extracellular matrix and tight junction proteins, and is produced by astrocytes, microglia, endothelial cells, and infiltrating leukocytes in response to oxidative stress and neuroinflammation [59]. MMP-9 rises early after acute cerebral injury, with peak activity commonly reported within 24-48 hours, temporally aligning with BBB permeability changes [47, 59, 60].

No clinical studies have directly tested circulating MMP-9 against MRI-defined remote DWI after ICH. Existing human evidence supporting MMP-9 as a biomarker largely derives from related ischaemic stroke and haemorrhagic transformation and therefore remains indirect for the specific question of post-ICH secondary ischaemic lesion detection [47, 59, 60].

Mechanistically, MMP-9 has stronger pathway alignment with post-ICH microvascular injury than distal inflammatory markers because it has been implicated in vascular and BBB structural injury. These processes may be relevant to endothelial dysfunction and microvascular impairment proposed to underlie remote DWI lesions after ICH [47,59,60].

In spontaneous ICH, haematoma toxicity, iron deposition, oxidative stress, and inflammatory signalling can upregulate MMP-9 via NF-κB and reactive oxygen species–dependent pathways, providing biological plausibility for involvement in secondary ischaemic phenomena [47, 59, 60].

Importantly, MMP-9 differs from upstream inflammatory markers (e.g., CRP, IL-6) because experimental studies suggest that it contributes to structural vascular injury rather than serving solely as an integrative inflammatory signal [59, 60]. This positions MMP-9 as a potential mechanistic bridge between inflammation, endothelial dysfunction, and post-ICH cerebral ischaemia. However, existing clinical evidence supporting MMP-9 as a diagnostic serum

marker remains indirect and largely extrapolated from ischaemic stroke and thrombolysis-associated haemorrhagic transformation studies [47, 59, 60].

Overall, MMP-9 represents one of the most mechanistically aligned circulating candidates for post-ICH secondary ischaemic injury but remains unproven diagnostically. Prospective MRI-linked studies with predefined lesion phenotypes and serial sampling are required before clinical translation can be considered. Therefore, current evidence remains insufficient to support MMP-9 for lesion-specific identification of remote DWI lesions after ICH.

### *Lactate dehydrogenase (LDH)*

Lactate dehydrogenase (LDH) is a ubiquitous cytosolic enzyme involved in anaerobic glycolysis and is released into the circulation following cellular membrane disruption and metabolic failure [70]. In acute ICH, elevated serum LDH likely reflects systemic and tissue-level injury burden rather than a brain-specific process [63].

One retrospective cohort study in spontaneous ICH reported that higher admission serum LDH was independently associated with remote DWI lesions, defined as infarct-like lesions occurring ≥20 mm from the primary haematoma [64]. An LDH threshold of ≥191 U/L predicted remote DWI lesions with an area under the curve of 0.74 and a high negative predictive value (94.2%), remaining significant after adjustment for age, blood pressure, haematoma volume, and intraventricular haemorrhage [64]. This study provides direct evidence of an association between a circulating marker and an imaging-defined secondary ischaemic lesion phenotype after ICH; however, the findings require external validation in independent cohorts.

Mechanistically, LDH is not lesion-specific and does not directly reflect the upstream mechanisms proposed to contribute to remote DWI lesion development, including endothelial dysfunction, autoregulatory failure, microvascular thrombosis, and BBB disruption [63]. Its association is therefore more plausibly interpreted as reflecting global metabolic stress and cumulative injury burden accompanying the conditions under which remote DWI lesions occur, rather than a causal or spatially informative signal [63, 64].

Overall, LDH is currently the only circulating marker with direct reported association with imaging-defined remote DWI lesions after ICH. However, its lack of brain specificity and vulnerability to extracranial confounding limit standalone diagnostic use. If externally validated, LDH may serve as a screening or enrichment marker within a multi-marker strategy rather than a lesion-specific diagnostic test. Nonetheless, current evidence is insufficient to support routine clinical use of LDH for identifying remote DWI lesions after ICH.

## 3. Coagulation and fibrinolysis

### *D-dimer*

D-dimer is a fibrin degradation product reflecting activated coagulation and fibrinolysis and is influenced by multiple extracranial conditions [55]. No previous studies have directly evaluated D-dimer for identifying or predicting imaging-defined secondary ischaemic lesions after acute ICH. Although D-dimer has been studied for hyperacute stroke classification and may help differentiate ischaemic stroke from intracerebral haemorrhage in settings where imaging is delayed [56], this evidence does not address post-ICH remote DWI lesion detection. When combined with GFAP and LVO scores, D-dimer shows poorer performance in diagnosing LVO stroke compared with GFAP alone [41, 65]. D-dimer is also highly confounded by infection, malignancy, atrial fibrillation, and venous thromboembolism, limiting lesion specificity [55].

Mechanistically, D-dimer may reflect systemic prothrombotic states that could plausibly accompany microvascular thrombosis after ICH [55], but its lack of specificity and lack of MRI-linked validation preclude diagnostic application for post-ICH secondary ischaemia.

To date, no studies have directly evaluated circulating D-dimer against MRI-defined remote DWI lesions after acute ICH. Accordingly, D-dimer cannot currently be recommended for detecting remote DWI lesions after ICH.

## 4. Cardiac and haemodynamic stress markers

### *N-terminal pro-B-type natriuretic peptide (NT-proBNP)*

N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a cleavage fragment released by cardiomyocytes in response to haemodynamic stress and neurohumoral activation and is strongly influenced by atrial fibrillation, heart failure, and hypertension [21, 39]. It is well-established as a marker associated with cardioembolic stroke mechanisms and has been evaluated in acute stroke classification pathways [33, 56, 58].

No previous studies have evaluated NT-proBNP as a diagnostic marker for imaging-defined secondary ischaemic lesions after acute ICH. Existing evidence relates to stroke subtype differentiation and aetiological inference rather than lesion-specific detection after ICH [56, 58].

Mechanistically, NT-proBNP reflects extracranial cardiac stress and cardioembolic propensity rather than the local microvascular and endothelial processes hypothesised to generate remote

DWI lesions after ICH. As such, any association with post-ICH ischaemic phenomena would be indirect and heavily confounded by cardiovascular co-morbidity [21].

Overall, NT-proBNP is not supported as a diagnostic serum marker for secondary ischaemic lesions after ICH.

### Summary of diagnostic serum markers

Despite extensive investigation, current evidence does not support routine serum testing for the identification of remote DWI lesions in acute ICH work-up [Table 1]. Most available studies rely on peripheral venous serum, which may dilute brain-specific signals and introduce extracranial confounding. It is also important to consider whether this sampling site influences biomarker detectability. While cerebrospinal fluid or jugular venous sampling could theoretically provide closer proximity to cerebral pathophysiology, these approaches are invasive, not routinely feasible in acute ICH, and lack validation against MRI-defined lesion phenotypes.

The principal translational limitation is that most biomarkers capture global injury or systemic stress rather than the focal microvascular processes presumed to generate remote DWI lesions after ICH [21,61-64]. Furthermore, because BBB disruption occurs early and extensively within the primary haemorrhagic lesion [5,21,29], circulating brain-derived biomarkers are likely to be dominated by signals originating from the haematoma and surrounding injured tissue. Any contribution from small, remote ischaemic lesions may therefore be difficult to distinguish from the substantially larger biomarker signal generated by the primary haemorrhage. This challenge is compounded by the fact that many candidate biomarkers are strongly associated with haematoma volume, perihaematomal oedema, intraventricular extension, and overall haemorrhage severity [61-64,102,112,114]. Consequently, biomarker changes potentially attributable to remote DWI lesions may be difficult to dissociate from the biological effects of the primary haemorrhage itself.

A further conceptual limitation is that no validated biomarker equivalent to cardiac troponin exists for focal cerebral ischaemia [21,69,70]. Most candidate biomarkers reflect non-specific injury, inflammatory, or vascular processes and are therefore lack the pathological specificity required to identify remote DWI lesions.

An important consideration is that established MRI markers of cerebral small vessel disease, including cerebral microbleeds, white matter hyperintensities, and composite small-vessel-disease burden scores, have demonstrated associations with subsequent cerebrovascular events after ICH [13,14,16] The evidence supporting these imaging markers is currently stronger than

that available for any circulating biomarker reviewed here. Consequently, any future serum biomarker intended for risk stratification or detection of secondary ischaemic injury after ICH would need to demonstrate incremental value beyond established imaging markers before clinical implementation could be justified.

Based on the evidence reviewed, secondary ischaemic injury after ICH is best conceptualised as a hypothetical multistage cascade. Firstly, vascular and BBB injury may result from haemorrhage-related mechanical stress and blood product toxicity and may contribute to endothelial dysfunction and barrier breakdown. Inflammatory amplification and oxidative stress follow characterised by innate immune activation and cytokine-driven endothelial activation. These upstream processes converge on microvascular failure, including impaired cerebral autoregulation, vasoconstriction, leukocyte and platelet adhesion, and prothrombotic states.

Although best characterised in subarachnoid haemorrhage-related delayed cerebral ischaemia, nitric oxide signalling has been proposed as a potential contributor to post-ICH microvascular dysfunction through haemoglobin-mediated nitric oxide scavenging, oxidative stress-related endothelial injury, and impaired vasoreactivity [5]. Together with endothelial dysfunction, inflammatory activation, and impaired microvascular perfusion, these mechanisms may contribute to the development of remote DWI lesions after ICH [15,16,19,20]. However, this proposed cascade remains a conceptual framework rather than a validated biological model, as supporting evidence is largely derived from experimental studies and related cerebrovascular conditions, and has not been prospectively validated using paired biomarker and MRI data in ICH.

Current candidate biomarkers align with discrete components of this pathway but not the full cascade. Inflammatory markers (such as CRP, IL-6, NLR) reflect systemic immune activation yet lack spatial specificity. Vascular and BBB-related markers (such as MMP-9 and D-dimer) are mechanistically plausible but remain insufficiently validated against lesion defined imaging endpoints. Metabolic injury markers (such as LDH) reflect downstream cellular injury without discriminating the mechanism or location. Finally, neuronal injury markers (such as serum NfL) quantify cumulative neuroaxonal damage but do not localise secondary ischaemia or provide insight into the mechanisms underlying remote DWI lesions.

Accordingly, future research should move beyond single-marker strategies toward temporally resolved biomarker panels that sample distinct stages of the post-ICH injury cascade, including vascular and BBB disruption, inflammatory–thrombotic activation, microvascular perfusion failure, and downstream neuronal injury. These panels must be validated against prespecified

MRI-defined lesion phenotypes using early and follow-up DWI. Such integrated biomarker–imaging frameworks offer the most credible path toward identifying patients at highest risk of secondary cerebral ischaemia and informing personalised haemodynamic and anti-inflammatory management strategies after ICH [66].

## Prognosis-focused serum markers

Prognostication after acute ICH is crucial for guiding treatment decisions, informing goals of care, and predicting recovery trajectories [67]. Prognostic tools such as the ICH score, which integrates clinical variables (age and Glasgow Coma Scale) with imaging features (haemorrhage volume, location, and presence of intraventricular haemorrhage), are routinely used in clinical practice to predict 30-day mortality [68]. More recently, serum biomarkers have been increasingly investigated as potential adjuncts to clinical and imaging-based scores, with proposed roles in prognostic risk stratification, treatment guidance, and clinical trial design [69]. However, whether serum biomarkers improve prognostication specifically in ICH patients with coexisting remote DWI lesions remains uncertain.

A broad range of serum biomarkers has been explored in ICH, with the most extensively studied categories including inflammatory, oxidative stress-related, and neuron- or astrocyte-specific markers [70]. These biomarkers are thought to reflect secondary brain injury associated with presence of blood in the brain parenchyma, including neuroinflammation, BBB disruption, neuronal and glial injury [71, 72]. Many of these mechanisms overlap biologically with pathways implicated in the development of remote DWI lesions, providing a rationale for investigation [5, 20].

### *Inflammatory biomarkers*

Inflammatory biomarkers have been most consistently studied in relation to prognosis after ICH, reflecting the role of neuroinflammation in secondary brain injury [71]. Commonly investigated blood-borne markers include total white blood cell count, neutrophils, lymphocytes, monocytes, and derived indices such as the NLR [69]. Several studies report associations between elevated inflammatory markers and worse functional outcomes, whereas others demonstrate no independent prognostic value after adjustment for established clinical and imaging predictors [73, 74].

For example, elevated NLR has been linked to poor 30-day functional outcomes and an increased risk of perihaematomal oedema expansion in some cohorts [73]. In contrast, other studies have failed to show an independent association between higher WBC, neutrophil count, or NLR and adverse outcomes [74]. Markers such as monocyte count and CRP have also been independently associated with increased odds of 30-day mortality in observational studies [75, 76]. However, these markers are non-specific and may be influenced by concurrent infection, aspiration, comorbidity burden, and overall severity of critical illness [77, 78].

Importantly, studies that have examined inflammatory markers in relation to DWI ischaemic lesions after ICH have largely focused on predicting lesion occurrence rather than clinical outcome [79]. For example, NLR has been associated with the presence of remote DWI lesions in some studies [74,80]. However, this represents a diagnostic rather than prognostic association. Available studies do not demonstrate that NLR predicts functional outcome or mortality specifically among patients with remote DWI lesions after ICH. As such, current evidence does not support the use of inflammatory biomarkers for prognostication in this subgroup of patients [69].

Beyond conventional inflammatory markers, mediators such as S100 calcium-binding protein A12 (S100A12) [81], cluster of differentiation 163 (CD163) [82], soluble CD 40 ligand (sCD40L) [83], YKL-40-chitinase-3-like protein 1 (YKL-40) [84], and gelsolin [85] have been associated with poor long-term functional outcomes and mortality in ICH. While these may reflect more specific immune pathways, evidence remains early and inconsistent, and their relationship to DWI lesions has not been evaluated**.**

### *Oxidative biomarkers*

Oxidative stress occurs as part of secondary injury after ICH and is characterised by haem-containing blood product release, iron toxicity, and reactive free radical generation leading to tissue injury [5]. Increased levels of thioredoxin (TRX), 8-iso-prostaglandin F2α (8-iso-PGF2α), and 8-hydroxy-2′-deoxyguanosine (8-OHdG) have been associated with poor long-term functional outcome and increased mortality [86, 87]. Other potential markers, including malondialdehyde, F2-isoprostanes, and 4-hydroxynonenal, are elevated after ICH and have been associated with larger haematoma volume and worse functional outcomes [87, 88, 89]. Nevertheless, these markers lack specificity for ICH, are influenced by systemic illness, and are measured using non-standardised methods [69].

To date, oxidative biomarkers have not been shown to predict prognosis specifically in ICH patients with DWI ischaemic lesions. Although some studies have explored biomarker associations with remote DWI lesion occurrence, these represent diagnostic associations rather than prognostic. No studies have demonstrated that oxidative biomarkers predict disability, mortality, or other clinical outcomes specifically among patients with remote DWI lesions after ICH. Therefore, their relevance to DWI-specific prognostication remains unproven.

### *Neuron and astrocyte-specific biomarkers*

Neuron and astrocyte specific serum biomarkers reflect structural brain injury and BBB disruption after ICH. Commonly studied markers include S100B [90] and GFAP (astrocytic) [91], and NSE, neurofilament light [92] and heavy chains, tau, myelin basic protein (MBP), and ubiquitin carboxy-terminal hydrolase L1 (UCH-L1) (neuronal) [93]. Systematic review evidence links higher levels of these biomarkers with worse outcomes, particularly mortality and poor functional outcome using the modified Rankin Scale (mRS), most often assessed at 90-180 days [69].

However, no previous studies have systematically examined whether neuron- or astrocyte-specific biomarkers predict functional outcome or mortality among patients with remote DWI lesions after ICH. Consequently, their prognostic utility within this subgroup remains unproven.

## Prognostic Blood Biomarkers for Haematoma Expansion

### *Serum calcium*

Serum calcium is an important biomarker in ICH and may influence bleeding progression through effects on coagulation and vascular stability [21]. Observational studies show that admission hypocalcaemia is linked to larger haematoma volume, greater risk of haematoma expansion, and worse outcomes (higher mortality and poorer functional recovery), with similar findings reported for both total and ionised calcium [94, 95].

In contrast, serum calcium has not been shown to predict DWI ischaemic lesion occurrence after ICH, and no studies have evaluated whether serum calcium predicts functional outcome or mortality specifically among patients with remote DWI lesions. Further studies are needed to clarify its potential role in this subgroup.

### *Serum magnesium*

In previous retrospective studies, admission serum magnesium shows a consistent relationship with ICH severity and bleeding progression: lower magnesium is linked to worse admission ICH score**,** higher systolic blood pressure, larger baseline haematoma volume, and in one study greater haematoma expansion and worse 3-month functional outcome [96, 97]. However, these studies focus on haemorrhage severity and outcomes rather than ischaemic injury.

There is currently limited evidence that serum magnesium predicts remote DWI lesion occurrence after ICH, and no studies have demonstrated that serum magnesium predicts clinical outcomes among patients with remote DWI lesions.

### *Serum LDL cholesterol*

Previous studies suggest that lower low density lipoprotein cholesterol (LDL-C) is associated with a higher risk of ICH, greater risk of haematoma expansion, and poorer functional outcomes [98]. In contrast, LDL-C has not been established as a predictor of post-ICH DWI lesion occurrence. In available DWI-lesion cohorts, lipid-related variables such as hypercholesterolaemia have not emerged as key associated factors [15,99]. Furthermore, no studies have evaluated whether LDL-C predicts functional outcome or mortality specifically among patients with remote DWI lesions after ICH. Therefore, its prognostic relevance within this subgroup remains unknown.

### *APOE genotype*

Apolipoprotein E (APOE) genotype has been independently associated with recurrent ICH, ischaemic stroke, dementia, and gait impairment after ICH, and earlier studies suggest that APOE2 is linked to haematoma expansion in lobar ICH/probable CAA and poorer outcomes [100]. More recent MRI studies show that APOE2 and 4 are associated with markers of cerebral small vessel disease, cerebral microbleeds, subcortical spots, and enlarged perivascular spaces [101]. However, the relevance of APOE genotype to remote DWI lesions after ICH remains unclear, and there is currently no evidence that APOE genotype predicts clinical outcomes among patients with these lesions.

### *Urinary biomarkers*

More recently, non-invasive approaches using urinary biomarkers have been explored in acute ICH. Observational studies demonstrate that urinary detection of brain injury markers such as

GFAP, NfL, UCH-L1, and total tau is feasible and may improve prediction of in-hospital mortality and 3-month functional outcome [117, 118]. In these studies, biomarker levels primarily reflect overall brain injury severity and are associated with baseline lesion volume rather than dynamic haemorrhagic or ischaemic processes. Importantly, haematoma expansion and post-ICH DWI-detected ischaemic lesions were not evaluated, and there is currently no evidence that urinary biomarkers improve prognostication in patients with remote DWI lesions after ICH.

## Serum inflammatory markers of haematoma oedema

### *CRP*

CRP is an acute-phase reactant and one of the most widely studied inflammatory serum markers in ICH. Higher CRP in the acute phase has been associated with larger haematoma volume, greater perihaematomal oedema, and worse clinical outcomes [102, 103]. In a prospective multicentre study of spontaneous ICH, CRP was measured on admission and again at 24, 48, and 72 hours; CRP at 48-72 hours showed the strongest prognostic signal and was independently associated with 30-day mortality and correlated with haematoma volume, supporting CRP as a marker of secondary inflammatory injury [102].

Although CRP may be higher in patients with post-ICH DWI ischaemic lesions, these associations relate to lesion occurrence rather than prognosis [104, 105]. There is currently no evidence that CRP predicts functional outcome or mortality among patients with remote DWI lesions after ICH.

### *Interleukins*

Pro-inflammatory cytokines rise after ICH as part of the secondary injury response. Key mediators include IL-1β, IL-6, IL-10, IL-11 and tumour necrosis factor alpha (TNF-α), which increase in both blood and cerebrospinal fluid [106, 107]. Higher levels of these cytokines are thought to contribute to ongoing brain injury by promoting inflammation, oxidative stress, and apoptosis, and by interfering with repair processes [108, 109].

Clinical studies examining IL-6 have also linked higher cytokine levels with larger perihaematomal oedema volumes, supporting a role for cytokine-driven inflammation [110]. Similarly, across clinical studies, raised cytokine levels have been linked with greater neurological severity and poorer outcomes, suggesting they reflect the intensity of secondary inflammatory injury after ICH [106, 107].

Current evidence relating inflammatory cytokines to remote DWI lesions after ICH is limited to studies of lesion occurrence rather than outcome prediction. Their prognostic value among patients with remote DWI lesions therefore remains unknown.

### *S100A12*

S100A12 is a calcium binding protein belonging to the S100 family. It serves as a signalling receptor for advanced glycation end products, Toll-like receptor (TLR)-4 and CD36, and has been in implicated vascular inflammation and endothelial dysfunction [111]. In acute ICH, higher admission serum S100A12 levels have been associated with greater baseline haematoma volume and higher clinical severity and have independently predicted early neurological deterioration and poor 3-month functional outcomes [112]. A recent review highlights S100A12 as a candidate inflammatory marker [113]. However, no studies have evaluated whether S100A12 predicts functional outcome or mortality among patients with remote DWI lesions after ICH. Consequently, its prognostic value in this subgroup remains unknown.

### *S100B*

A higher serum S100B in acute ICH has been associated with larger haematoma volume, greater perihaematomal oedema, and worse neurological severity and outcomes [114]. However, no studies have evaluated whether S100B predicts functional outcome or mortality specifically among patients with remote DWI lesions after ICH. Its prognostic value in this subgroup therefore remains unknown.

### *Progesterone*

Experimental mice models have suggested progesterone as a potential neuroprotective mediator in reducing secondary injury pathways, including neuroinflammation and brain oedema following ICH [115]. However, human evidence on ICH is limited and exploratory. A recent pilot study measured serum gonadal hormones, including progesterone, in the early phase after spontaneous supratentorial ICH and explored associations with 6-month functional outcomes [116]. The study did not establish progesterone as a validated prognostic biomarker or therapeutic target. Evidence relating progesterone to remote DWI lesions after ICH is currently lacking, and no studies have evaluated its prognostic value among patients with these lesions.

## Methodological limitations of the current evidence

Despite the breadth of biomarkers investigated for diagnostic and prognostic applications after ICH, several recurring methodological limitations constrain interpretation of the available evidence. First, most studies evaluating biomarkers and remote DWI lesions after ICH are retrospective, single-centre investigations with relatively small sample sizes, limiting statistical power and a high likelihood to selection bias [15,16,64]. Second, biomarker assessment is typically based on single time-point measurements despite the dynamic evolution of both circulating biomarkers and DWI lesions after ICH [15,16,19,21,69]. Third, there is considerable heterogeneity in MRI acquisition, timing, and definitions of remote DWI lesions, which complicates comparisons across studies and may contribute to inconsistent findings [15,16,18,19]. Furthermore, many candidate biomarkers are influenced by factors related to the primary haemorrhage itself, including haematoma volume, perihaematomal oedema, intraventricular extension, and overall disease severity, making it difficult to distinguish lesion-specific signals from markers of global injury [61-63,102,112,114]. Finally, few studies have incorporated serial MRI assessment or external validation cohorts, and the only biomarker directly associated with remote DWI lesions (LDH) remains supported by a single retrospective study [64]. Collectively, these limitations, together with the uncertain biological basis of remote DWI lesions after ICH, may explain why biologically plausible biomarkers have not demonstrated consistent lesion-specific diagnostic or prognostic utility.

## Guideline status and clinical implications

Current international guidelines do not recommend routine serum biomarker testing or routine MRI screening for the detection of remote DWI lesions after acute ICH [6,7]. This reflects the limited evidence linking circulating biomarkers to MRI-defined secondary ischaemic lesions and the uncertain clinical significance of these lesions [15,16,19]. The studies reviewed suggest that most candidate biomarkers reflect global brain injury, systemic inflammation, haemorrhage severity, or overall prognosis rather than lesion-specific secondary ischaemia. Consequently, there is currently insufficient evidence to support their routine clinical use.

At present, detection of remote DWI lesions does not alter standard ICH management, which remains guided by established clinical and imaging evidence [6,7,17]. Nevertheless, remote DWI lesions have been associated with an increased risk of subsequent cerebrovascular events and poorer functional outcomes after ICH [16,17,19]. Although no biomarker-guided treatment strategy currently exists, reliable identification of patients at increased risk of these lesions

could potentially improve risk stratification, support selection for advanced imaging, and facilitate enrolment into future mechanistic and interventional studies [66,119,120]. However, these potential applications remain investigational and require prospective validation before implementation in routine clinical practice [6,7].

## Why is this article important?

Despite pre-clinical and translational advances, the ESO 2025 guidelines do not recommend routine DWI or specific serum testing for the detection of ischaemic lesions in the management of ICH. This review critically evaluates the available literature to clarify the evidence underlying this position. Specifically, we examine whether serum investigations add clinical value in the assessment of remote DWI lesions after acute ICH.

## Conclusion and Future Directions

Current evidence does not support routine serum investigation for the detection of secondary ischaemic lesions in the acute work-up of ICH. Although numerous circulating biomarkers have been studied in ICH, none have demonstrated consistent diagnostic or prognostic value when evaluated against MRI-defined remote DWI lesions. Most biomarkers investigated to date reflect global brain injury, systemic inflammation, stroke subtype differentiation, or overall prognostic risk rather than the focal microvascular processes thought to underlie post-ICH secondary ischaemic injury. This aligns with current guideline positions, which do not recommend routine DWI or serum biomarker testing for this purpose.

A key limitation in the literature is that biomarkers have rarely been studied in designs that allow their relationship to MRI-defined secondary ischaemic lesions to be directly tested. Few studies have evaluated circulating biomarkers against prespecified MRI-defined remote DWI lesions phenotypes after ICH, and these are largely limited to single time-point measurements rather than serial sampling designs. As a result, it remains difficult to determine whether circulating biomarkers relate to microvascular injury or simply reflect overall disease severity. Recent developments in stroke research now make such studies feasible. For instance, studies conducted in the emergency setting demonstrate that early point-of-care biomarker sampling in ICH can be integrated into hyperacute care pathways, enabling temporally biomarker measurements that could be linked to subsequent MRI-defined lesion development [119]. Advances in proteomics, particularly the study of plasma-derived extracellular vesicles, suggest that circulating protein profiles may capture thrombo-inflammatory and coagulation-

related processes that differentiate stroke pathophysiology, suggesting a potential way to measure blood markers more closely aligned with microvascular injury than conventional single serum markers [66]. In parallel, contemporary biomarker frameworks emphasise that circulating markers should be evaluated alongside imaging and physiological data over time rather than in isolation [120]. The use of MRI markers, combined with automated imaging platforms, now allows quantitative extraction of imaging features at scale using large datasets [121].

## Proposed framework for future biomarker studies in ICH

To address the limitations of the current evidence base, future studies should incorporate the following elements:

### 1. Multi-marker biomarker panels

Given the heterogeneous and incompletely understood biology of remote DWI lesions after ICH, reliance on a single biomarker is unlikely to provide sufficient diagnostic accuracy. Future studies should evaluate panels incorporating markers of vascular and BBB injury, inflammation, thrombosis, and neuronal injury to capture multiple components of the proposed injury cascade [66,120].

### 2. Serial biomarker sampling

Most existing studies rely on single time-point measurements despite the dynamic evolution of both biomarkers and DWI lesions. Future studies should incorporate serial sampling during the hyperacute and early subacute phases (e.g., admission, 6, 24, and 72 hours) to characterise temporal biomarker trajectories and their relationship with lesion development [66,119].

### 3. Standardised MRI protocols and lesion definitions

There is currently significant heterogeneity in MRI acquisition, timing, and definitions of remote DWI lesions after ICH. Future studies should adopt standardised MRI protocols, including predefined imaging time windows and consensus definitions of remote DWI lesions, to improve comparability across studies and facilitate external validation [15,16,19].

### 4. Integration with haemodynamic and physiological monitoring

Future biomarker studies should be integrated with physiological measurements, including blood pressure trajectories, cerebral autoregulation indices, and other haemodynamic parameters. Such multimodal approaches may help clarify whether remote DWI lesions arise from impaired perfusion, endothelial dysfunction, inflammatory activation, or a combination of mechanisms [5,6,17].

**5. Prospective multicentre validation**

Promising biomarkers should be evaluated in adequately powered prospective multicentre cohorts with predefined imaging and clinical endpoints. External validation will be essential before any biomarker can be considered for clinical implementation or inclusion in future guideline recommendations.

**Statements**

**Acknowledgement**: None.

**Conflict of interest statement:** Thompson G. Robinson and Jatinder S. Minhas were members of the journal's Editorial Board at the time of submission.

**Funding sources:** This review received no specific funding. SSM is supported by a PhD studentship from the National Institute for Health and Care Research (NIHR) Leicester Biomedical Research Centre (BRC), United Kingdom. JKN and JSM are supported by a UKRI Future Leaders Fellowship [MR/Y016807/1]. JSM is supported by a Stroke Association Clinical Lectureship [SA SCLM23\100003]. JSM is supported by the National Institute for Health and Care Research (NIHR) Leicester Biomedical Research Centre (BRC). TGR is an emeritus NIHR Senior Investigator. TWO is supported by a Sir Henry Dale Fellowship jointly funded by the Wellcome Trust and the Royal Society (220204/Z/20/Z). The views expressed are those of the author(s) and not necessarily those of the Stroke Association, UKRI, NIHR or the Department of Health and Social Care. 

**Author contributions:** SSM, ASM and JSM conceptualised the review and conducted the literature synthesis. SSM and ASM drafted the initial manuscript. JKN, RBP, KTSP, TWO, CLW, ARPJ and TGR all contributed to critical appraisal of the evidence, provided important

intellectual input, and critically revised the manuscript. JSM provided senior oversight throughout manuscript development. All authors approved the final version for submission.

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